10/049,429

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
038602/0272		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US00/23744	30/08/2000	30/08/1999
International Patent Classification (IPC) or national classification and IPC C07K14/71		
Applicant NEW YORK UNIVERSITY SCHOOL OF MEDICINE et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☒ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
30/03/2001	19.04.2002
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Moonen, P Telephone No. +49 89 2399 8538

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/US00/23744

I. Basis f the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:
Description, pages:

1-627 as originally filed

Claims, No.:

1-89 as originally filed

Drawings, sheets:

1/26-26/26 as originally filed

Drawings, No.:

1-33 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 18, 28-57, 66, 68, 78-89.

because:

   ☒ the said international application, or the said claims Nos. 18, 43-51, 54-57, 68 and 78-86 relate to the following subject matter which does not require an international preliminary examination (*specify*): **see separate sheet**

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☒ no international search report has been established for the said claims Nos. 28-42, 52-53, 66, 87-89.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

   ☐ restricted the claims.

   ☐ paid additional fees.

   ☐ paid additional fees under protest.

   ☐ neither restricted nor paid additional fees.

2. ☒ This Authority found that the requirement of unity of invention is not complied and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:
   see separate sheet

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

   ☒ all parts.

   ☐ the parts relating to claims Nos. .

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	3-7, 9-17, 19-20, 58-65, 67-68, 70-77
	No:	Claims	1-2, 8, 21-27, 69
Inventive step (IS)	Yes:	Claims	
	No:	Claims	3-7, 9-17, 19-20, 58-65, 67-68, 70-77
Industrial applicability (IA)	Yes:	Claims	1-17, 19-27, 58-65, 67-77
	No:	Claims	

2. Citations and explanations
   see separate sheet

1. Reference is made to the following documents:

D1 Mohammadi & Hubbard; Crystal structure of an angiogenesis inhibitor bound to the FGF receptor tyrosine kinase domain EMBO J **7** (1998) 5896-5904 * (first page)

D2 Hubbard et al., Autoregulatory mechanisms in protein-tyrosine kinases, J Biol Chem **273** (1998) 11987-90 *

D3 Himanen et al., Crystal structure of the ligand-binding domain of the receptor tyrosine kinase EphB2; Nature **396** (1998) 486 * (first page)

D4 Ultsch et al., JMB **290** (July 1999) 149-159 * (first page)

D5 Wiesmann et al., Cell **91** (1997) 695-704 * (first page)

D6 Venkataraman et al., Molecular characteristics of FGF-FGFR-heparin-like complex, PNAS **96** (March 1999) 3658-63 *

D7 PELLEGRINI L ET AL: 'The role of heparin in the complex formation between fibroblast growth factor 2 and its high affinity receptor: Comparative modelling and biochemical studies.' BIOCHEMICAL SOCIETY TRANSACTIONS, vol. 26, no. 3, August 1998 (1998-08), pages 545-549, Meeting of the Biochemical Society;Southampton, England, UK; March 31-April 2, 1998

D8 PLOTNIKOV ALEXANDER N ET AL: 'Structural basis for FGF receptor dimerization and activation.' CELL, **98** (3 September 1999) 641-650

D9: PLOTNIKOV ALEXANDER N ET AL: 'Crystal structures of two FGF-FGFR complexes reveal the determinants of ligand-receptor specificity.' CELL, vol. 101, no. 4, 12 May 2000 (2000-05-12), pages 413-424

D10:PELLEGRINI LUCA ET AL: 'Crystal structure of fibroblast growth factor receptor ectodomain bound to ligand and heparin.' NATURE (LONDON), vol. 407, no. 6807, 2000, pages 1029-1034

D11:STAUBER DEBORAH J ET AL: 'Structural interactions of fibroblast growth factor receptor with its ligands.' PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES, vol. 97, no. 1, 4 January 2000 (2000-01-04), pages 49-54

* The documents D1-D6 were not cited in the international search report. Copies of the first pages of the documents have been supplied.

R Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

2. **Claims 18, 43-51, 54-57, 68 and 78-86** relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1 PCT.
All claims except claim 68 either relate to subject-matter being a mere presentation of information (see Rule 67.1(v) PCT), a computer program having no further technical feature (see Rule 67.1(vi) PCT), or the performing of a mental act (see Rule 67.1(iii) PCT). No opinion will therefore be established according to Article 34(4)(a)(i) PCT.

   Claim 68 is a method of treating a disease (see Rule 67.1(iv) PCT). Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of claim 68 (Article 34(4)(a)(i) PCT).

3. **Claims 28-42, 52-53, and 87-89** have not been searched (no search fees were paid). An examination is therefore also not carried out for these claims. With respect to **claim 66** it is noted that no meaningful search could be carried out.

Re Item IV

Lack of unity of invention

4. The present application claims one priority date (30.08.1999) of priority application US 60/151,810, designated henceforth P1. The subject-matter of P1 is much more limited in scope than the internationally filed application.

   It is for example noted that P1 only refers to the fibroblast growth factor receptor 1 (FGFR1).

5. D8-D11 are therefore fully citable as prior art with respect to subject-matting lacking the right of priority to P1. It is noted moreover that non-unity of invention arises from this lack of right of priority, as a common novel and inventive, special **technical f atur is missing b tw n th subj ct-matt r of claims 5 and 21**; see below.

6. A single general inventive concept (referred to in Rule 13 PCT and the PCT Preliminary Examination Guidelines Ch.III, 7) is therefore not recognisable in the absence of a common, special technical feature. A further non-unity is recognised between the subject-matter of **claims 58-65** referring methods of identifying a modulator of undefined receptor protein kinase function and the claims referring to the crystal structure of the extracellular domain of FGFR, e.g. **claims 1-20**. This also applies to **claims 67-68** referring to the receptor protein tyrosine activity, having no direct link to the crystal structures. In view of the time limits all searched claims are presently examined.

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

7. The presently examined application (partially text is taken from Wiesmann and de Voss in a minireview published in Structure, **7** (November 1999), R251-255) concerns the crystal structure of the known FGF-receptor (complex), a member of the family of receptor tyrosine kinases (RTKs), so named because of their intracellular tyrosine kinase domain. RTKs are activated through ligand-induced dimerization requiring heparan-sulfate-containing proteoglycans (like heparin), and recent **crystallographic studies** have revealed the mechanisms for some of the early intracellular processes at the atomic level (see **D1** and **D2**).

   Much less is known in the prior art about the molecular/structural details of the extracellular events: The ligand is monomeric FGF binding to the extracellular portion of cell-bound FGFRs usually consisting of three IgG-like domains.

8. **The crystal structures of several ligand-binding domains of receptor tyrosin kinases** have been disclosed in the prior art; those domains are of EphB2 (see **D3**), VEGFR1 (see **D4**; complex of ligand with receptor) and the Trks (see **D5;** domains having an immunoglobulin-like fold) are known: thus the subject-matter of **claims 1, 2, 8 and 69** in its broad scope is not novel.

   Homology modelling based in IL1 and its receptor have also predicted molecular characteristics of the FGF-FGFR-heparin-like complex (see **.g D6** and **D7).**

7. The subject-matter of **claims 3-7, 9-17, 19-20 and 70-77** is novel as no prior art referred to the crystallised ligand-binding domains of a FGFR (comprising a sulfated oligosaccharide). However, in view of the studies of closely related extracellular domains of receptor protein kinases the claimed subject-matter is obvious to the skilled person; he could and would carry out the crystallisation with the available methods of the ligand binding domains. It was already known that the Ig-like domain 1 is not essential for ligand binding (the domain is missing in a naturally occurring variant of FGFR1; see D7 and reference 3 and 4 of D7). The dependence of FGF binding on sulfated oligosaccharide was also well known.

   Therefore, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of claims 3-7, 9-17, 19-20 and 70-77 does not involve an inventive step (Rule 65(1)(2) PCT).

   Finally it is noted that the subject-matter of claims 70-77 is not entitled to the priority date.

8. The subject-matter of **claims 21-27** does not have the right of priority. Thus D8- D11 are available for citation. D9-D11 all refer to the structure of the ligand bindinding domain of FGFR2; e.g. D9 to the residues 147 to 366 complexed to FGF2 and said claims therefore **lack novelty** over e.g. D9, contrary to the requirements of Article 33(2) PCT.

9. The subject-matter of **claims 58-65, if** considered to be novel over the prior art referring to the three dimensional representations of the cytoplasmic domains, is obvious to the skilled person. The methods appear to be based on methods of the prior art (see D1 and D2). The same reasoning applies to **claims 67-68.**
   Therefore, the present application does not satisfy the criterion set forth in Article 33(3) PCT because the subject-matter of said claims does not involve an inventive step (Rule 65(1)(2) PCT).

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